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Clinicopathologic Findings in Congenital Aneurysms of the Great Vessels

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We describe the clinical, histopathologic, and angiographic findings in four children with congenital abnormalities of the great vessels of unknown cause, comprising either single or multiple arterial aneurysms, aortic/arterial dilatation, vessel tortuosity, or combinations of these abnormalities. Two children had early and severe respiratory distress due to aneurysmal compression of the trachea. All children had diffuse dilatation of several arteries, and two children also had tortuosity of multiple arteries. Progression of these abnormalities was clearly evident in one child, in whom diffuse vessel irregularity and tortuosity affected intra-abdominal, and intra and extra-cranial arteries. One child died at 5 years, while the other three have undergone successful surgical repair in the first 3 months of life and are now well, between age 2.5 and 7 years. The phenotype of each child appears unique but all have in common the rare finding of aneurysms of the aorta and main pulmonary artery. Congenital aortic aneurysms did not occur as an isolated finding in any of these children.

KEY WORDS: congenital aneurysms of the great vessels, arterial dilatation and tortuosity, connective tissue disorder, collagen, fibrillin, elastin

INTRODUCTION

Single or multiple congenital aortic aneurysms are rare. They may occur in the thoracic and/or abdominal aorta in association with other vascular abnormalities [Fricker et al., 1979; Skandalakis et al., 1960; Chen et al., 1976] including multiple peripheral and visceral aneurysms, or with non-cardiovascular birth defects, or in neonatal Marfan syndrome [Morse et al., 1990]. We report on four children with the rare combination of congenital aortic and pulmonary artery aneurysms. Each child has a distinct phenotype. They are presented together because they have manifestations in common and because of their rarity.

CLINICAL REPORTS

Case 1

A male infant was born at term to nonconsanguineous parents, after a pregnancy complicated by polyhydramnios and pre-eclampsia. The birth weight (BW) was 4,770 g (>95th centile) and length (BL) was 54.3 cm (95th centile). He was intubated immediately because of respiratory distress and treated for tachycardia with digoxin.

On examination the infant had a prominent forehead, widely open anterior fontanelle, bilateral proptosis, alternating exotropia, a thin upper lip, high narrow palatal arch, bifid uvula, submucous cleft of the soft palate, hirsute helices, micrognathia, postaxial hexadactyly of all limbs except the left foot, and bilateral talipes equinovarus. Additional anomalies included bilateral coronal synostosis, gracile long bones and ribs, flexion contractures of all digits on both hands with metacarpophalangeal subluxation/dislocation upon extension, elongated metacarpals, metatarsals and phalanges. There was ligamentous laxity, hyperextensibility of the metacarpophalangeal joints, dislocatable fingers, hips and knees, and genua valga.

The maternal grandfather had died of dissection of an abdominal aortic aneurysm. A great uncle had extra fingers.

Cardiac evaluation at age 1 week showed a small atrial septal defect, patent ductus arteriosus, dilated

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main pulmonary artery, dilated ascending aorta, and tortuous descending aorta. At thoracotomy a large patent ductus arteriosus was ligated and divided with resection of a large ductal aneurysm. Cardiac catheterisation and abdominal ultrasound study at 3 months showed a cervical aortic arch, tortuous thoracic aorta crossing over to the right at the level of the diaphragm, multiple aneurysms of the aorta (the longest distal to the origin of the renal arteries), aneurysm of the left subclavian artery, and a dilated superior mesenteric artery. Progressive dilatation of the aortic root from 1.7 cm to 2.0 cm occurred over the next 6 weeks. No further details are available.

Case 2

A male infant born at term to non-consanguineous parents had a BW of 4,600 g (>95th centile), cleft of the soft palate, and a cardiac murmur. Echocardiogram at birth showed a dilated aortic root. Ophthalmologic examination showed a hamartoma of the retina. Subsequently he had chronic constipation, strabismus, and developed a marked pectus excavatum. ECG showed an intraventricular conduction delay. An echocardiogram and magnetic resonance imaging (MRI) scan at age 5 years showed dilatation of the aortic root, proximal aorta and proximal pulmonary artery, and a patent ductus arteriosus. He was treated with atenolol but died suddenly from a presumed arrhythmia at age 5 years. Chromosomes were normal, 46,XY.

Autopsy findings included asymmetric frontal bossing, a prominent occiput, telecanthus, large posteriorly angulated ears, and a short philtrum. There was mild cardiomegaly with enlargement of the right atrium and right ventricle. The pulmonary valve cusps were abnormally thin. The proximal and segmental pulmonary arteries were diffusely dilated and abnormally thin walled. The pulmonary, mitral, and aortic valve circumferences were enlarged and abnormally compliant. The circumferences of the ascending aorta, descending aorta, main, right, and left pulmonary arteries were 6, 2.2, 5.7, 2.5, and 2.5 cm, respectively. There was aneurysmal dilatation of the sinuses of Valsalva. The coronary ostia were slit-like, with broad-based aneurysmal dilatation of the anterior aspect of the aortic isthmus and mild thinning of its wall. The main coronary arteries were diffusely enlarged and their walls were abnormally soft. The right brachiocephalic and left vertebral arteries were thin walled, tortuous, and diffusely enlarged. There was a 4 mm tortuous patent ductus arteriosus. The descending aorta and its branches were normal. Histologic examination showed significant lymphocytic myocarditis which may have precipitated an arrhythmia and death. The arterial walls showed variable non-occlusive intimal hyperplasia, thinning and degeneration of the media, and accumulation of mucopolysaccharide material. Elastin stains showed decreased, fragmented elastic fibres. Electron microscopy of the aorta was non-contributory. Other findings included mobility of the large bowel due to incomplete fixation, and a unilateral parietal dermoid cyst of the skull. The brain was normal.

Case 3

A male infant born at term was the second child of non-consanguineous parents. BW was 3,410 g (50th centile). A paternal niece had tetralogy of Fallot and a paternal female first cousin had aneurysmal dilatation of a cerebral vessel, confirmed on computerised axial tomography (CT) scan.

There was severe respiratory distress and cyanosis from birth. Echocardiography and cardiac catheterisation showed a dilated right atrium, a thickened tricuspid valve which was regurgitant and stenotic, a dilated and misshapen right ventricle, and a mildly thick pulmonary valve (systolic gradient 6 mm Hg). Pulmonary arteriography (Fig. 1A) showed massive dilatation of the pulmonary trunk and severe pulmonary regurgitation. Despite the latter, pulmonary artery pressure was 55/30 (mean 40) mm Hg. There was a significant right to left shunt at atrial level. The left ventriculogram (Fig. 1B) showed an intact ventricular septum, a normal aortic valve, and marked dilatation of the ascending aorta and aortic arch. There was left to right shunting through the duct but due to the high pulmonary vascular resistance and pulmonary and tricuspid regurgitation, there was progressive retrograde opacification of the right ventricle, right atrium and then left atrium, with very little flow to the lungs. On echocardiography, the aortic root diameter (ARD), ascending aortic diameter, and main pulmonary and left pulmonary artery diameters were 2.1, 1.9, 2.2, and 1 cm, respectively, and tricuspid valve diameter 1.2 cm.

He was treated with prostaglandin E1 and dopamine and, at age 3 weeks, underwent surgery because of unrelenting extrinsic airway compression by the aneurysmal great arteries. Operative findings included aneurysmal dilatation of the ascending aorta, aortic arch, and upper half of the descending aorta; ectasia of the innominate, left subclavian and right coronary arteries and aneurysmal dilatation of the main, proximal right and left pulmonary arteries. The pulmonary and tricuspid valves were dysplastic, mildly stenosed, and incompetent. There was a secundum atrial septal defect. The trachea was severely compressed. The entire ascending aorta and upper half of the descending aorta were replaced with a 12 mm dacron hemishield tube graft. The patent ductus arteriosus was ligated, the pulmonary valve and trunk replaced with a 13 mm aortic homograft, the atrial septal defect sutured and tricuspid valve commisurotomy was performed. Histologic examination of the resected aorta (Fig. 2) showed normally ordered elastin fibres with a minimal increase in interstitial glycosaminoglycan deposition. There was mild fibrointimal hyperplasia.

At age 2 years, echocardiogram and cardiac catheterisation showed a significantly enlarged right atrium and ventricle, severe tricuspid regurgitation, and moderate pulmonary homograft valve regurgitation. The right pulmonary artery diameter distal to the homograft was dilated, measuring 1.8 cm. The aortic root was slightly enlarged (1.8–2.0 cm) proximal to the graft. There was no aortic regurgitation. Distal to the graft, there was mild dilatation and tortuosity of

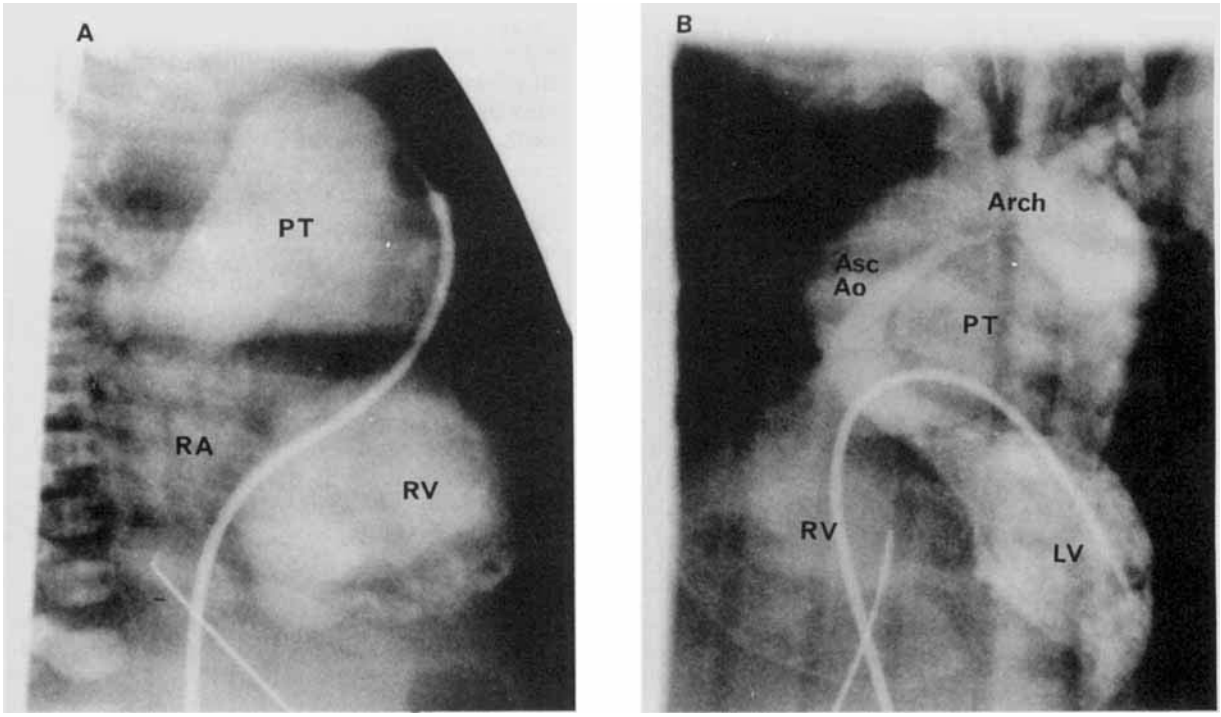

Fig. 1. Case 3 at day 1. **A:** Lateral pulmonary arteriogram showing massive dilatation of the pulmonary trunk (PT). **B:** Left ventriculogram showing marked dilatation of the ascending aorta (AscAo) and aortic arch. RA, right atrium; RV, right ventricle; LV, left ventricle.

the proximal descending thoracic aorta. The ARD showed progressive dilatation (1.95 and 2.1 cm, at 3 years 8 months and 5 years, respectively). Treatment consisted of daily aspirin. The use of beta-blockers was contraindicated because of severe asthma.

At the age of 3.5 years, his height was on the 3rd centile and weight was on the 10th centile. There was no arachnodactyly, joint hyperextensibility, dolichostenomelia, scoliosis, lens dislocation, or skin abnormality. He had pes planus and severe high frequency sensorineural deafness (most likely attributable to neonatal hypoxia), with associated speech delay. Chromosomes were normal, 46,XY.

Case 4

Details of the pregnancy, delivery, early neonatal period, and family history were unknown for Case 4, an adopted female infant who presented with symptoms of airway compression in the first 1–2 months of life. Cardiac catheterisation and angiography at age 6 weeks showed marked aneurysmal dilatation of the ascending aorta, and dilatation of the proximal aortic arch and innominate artery (Fig. 3A). There was massive dilatation of the pulmonary trunk (Fig. 3B) beyond the pulmonary valve, left pulmonary artery origin stenosis, stenosis of the right pulmonary artery beyond its origin, a huge ductal diverticulum on the pulmonary artery, and moderate pulmonary regurgitation. There was no pulmonary stenosis. The remaining valves were normal. She was treated with propanolol.

At 2.5 months of age, she underwent shortening and extensive aneurysmorrhaphy of both the ascending aorta and pulmonary trunk, with pericardial patch repair of the stenotic left pulmonary artery and dilatation of the right pulmonary artery. The aorta and pulmonary trunk were thick walled (the pulmonary trunk was thicker than the aorta), and the aortic layers came apart easily.

Life-threatening episodes of respiratory obstruction prompted cardiac re-catheterisation at 7 months of age. Aortography showed an even larger aneurysm of the ascending aorta and innominate artery (Fig. 3C). The ascending aorta was massive, pushing the bifurcation of the innominate artery superiorly, and the aortic valve inferiorly to the level of the xiphisternal junction. There was significant residual tracheal narrowing and obstruction from compression by the aorta. From the mid-arch, the aorta was normal.

At reoperation at age 8 months, findings included massive recurrent aneurysm of the ascending aorta, extending into the innominate artery. There was restenosis of the left pulmonary artery and a prominent ductal diverticulum extending upwards and to the left. The right atrial appendage and lower abdominal aorta were cannulated for cardiopulmonary bypass. The ascending aorta, proximal innominate artery and proximal arch were excised and replaced by a 14 mm collagen impregnated dacron graft. The innominate bifurcation was anastomosed end to side to the base of the left common carotid artery. The left main pulmonary artery origin was dilated. Post-operatively she developed left up-

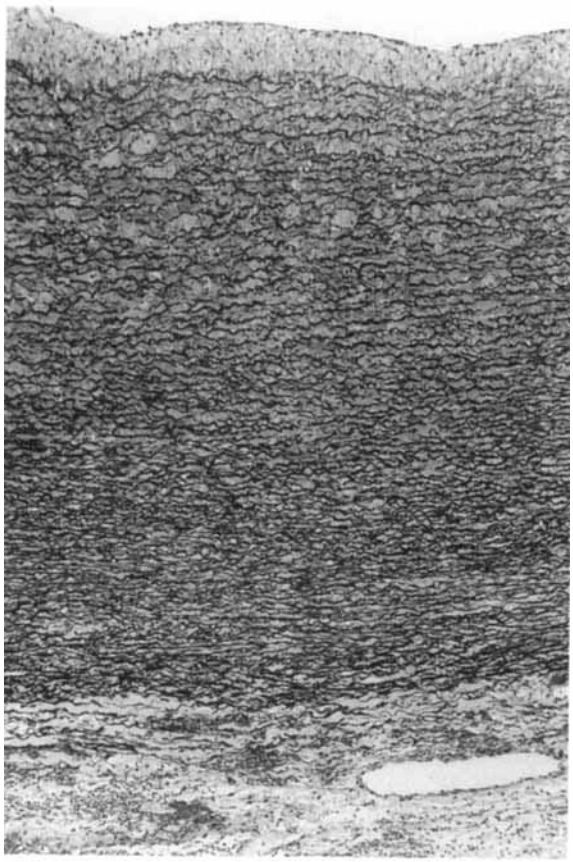

Fig. 2. Case 3. Histological section from the aorta showing mild fibrointimal hyperplasia. (Movatt pentachrome stain, magnification ×110.)

per lobe collapse and consolidation which was considered to be due to compression by the aneurysmal ductal diverticulum.

Echocardiograms at age 7, 20, 30, 46, and 76 months showed an ARD of 1.8, 2.65, 2.74, 2.9, and 3 cm, respectively. Cineangiography at age 39 months showed an unobstructed aortic graft and a redundant aortic arch (Fig. 3D). The pulmonary trunk (diameter 2.2 cm) and proximal right and left branches were significantly dilated. The abdominal aorta was slightly tortuous but not dilated. The major abdominal arteries were tortuous and dilated (Fig. 3E). The patient was maintained on atenolol.

Histologic examination of the aorta (Fig. 4A) and pulmonary artery (Fig. 4B) from the initial surgery showed marked disruption of elastic fibres with an increase in deposition of interstitial glycosaminoglycans and marked thickening of the arterial intima. Large elastic fibres were markedly reduced in number and small elastic fibres were highly irregular in distribution.

Ultrasound study of the right common and internal carotid arteries at age 4.5 years of age showed marked tortuosity and mild fusiform dilatation of the right common carotid artery. The left common carotid artery showed less marked tortuosity. A cerebral angiogram at age 5.5 years showed extreme tortuosity and dilatation of intra- and extra-cranial arteries (Fig. 5A,B).

At age 5 years, her growth parameters were normal. She had prominent eyes, a bulbous nasal tip, a prominent premaxilla, a highly arched palate, micrognathia, generalised mild joint hypermobility, and velvety smooth skin with normal scarring.

MATERIALS AND METHODS

Studies of fibrillin-1, and Types I and III collagen metabolism were performed on cultured dermal fibroblasts from all patients. Skin biopsies were obtained after appropriate parental consent and dermal fibroblasts explanted using standard techniques [Milewicz et al., 1992]. Dermal fibroblasts were used to study the synthesis, secretion and matrix incorporation of fibrillin-1 by metabolically labelling fibrillin-1 with [^{35}S] cysteine and established pulse-chase protocols [Milewicz et al., 1992]. Dermal fibroblasts were also used to study the synthesis and secretion of type I, proα(III) and type III collagen using established protocols [Bateman et al., 1988].

In addition, collagen crosslinking was assessed in cultured fibroblasts from Case 4 because of the striking similarity between the arterial abnormalities in this patient and those seen in Menkes disease, a disorder of copper metabolism [Procopis et al., 1981]. Collagen crosslinking was assessed in cultured fibroblasts where collagen matrix formation and maturation was induced by long-term culture for 20 days with ascorbate as previously described [Bateman and Golub, 1994]. Collagen was pulse-labelled with 50 μCi [2,3^{3}H-proline] for 24 hours and then chased in an isotope-free medium for a further 24 hours. Deposition of labelled collagen into the mature crosslinked collagenous matrix was assessed by a serial extraction with neutral salt buffer (to extract newly synthesised non-crosslinked collagen) followed by extraction with 0.5 M acetic acid and then pepsin (to extract the progressively more crosslinked collagens). The proportions of collagens in each of the fractions was quantified by SDS/polyacrylamide gel electrophoresis [Bateman et al., 1988].

Fluorescent in situ hybridisation was performed in Case 4 to exclude the possibility of an elastin gene deletion. The elastin Williams syndrome chromosome region (WSCR) Probe (Oncor) was used on cultured dermal fibroblasts. The cells were processed according to the Oncor protocol, using the alternative formamide wash method. A positive signal was indicated by a fluorescent signal present on both chromatids of a metaphase chromosome 7. A nondeleted sample was indicated by the presence of a fluorescent signal on both chromatids of both chromosome 7 homologues.

RESULTS

A summary of clinical findings in Cases 1–4 and arterial histology in Cases 2–4 is presented in Tables I and II, respectively. Detailed biochemical evaluation of collagen produced by cultured dermal fibroblasts failed to identify any abnormalities of type I and III collagen synthesis in any of the cases. Electrophoretic analysis of the collagen also demonstrated that there were no detectable structural abnormalities. Results of similar analyses of fibrillin were normal in all cases.

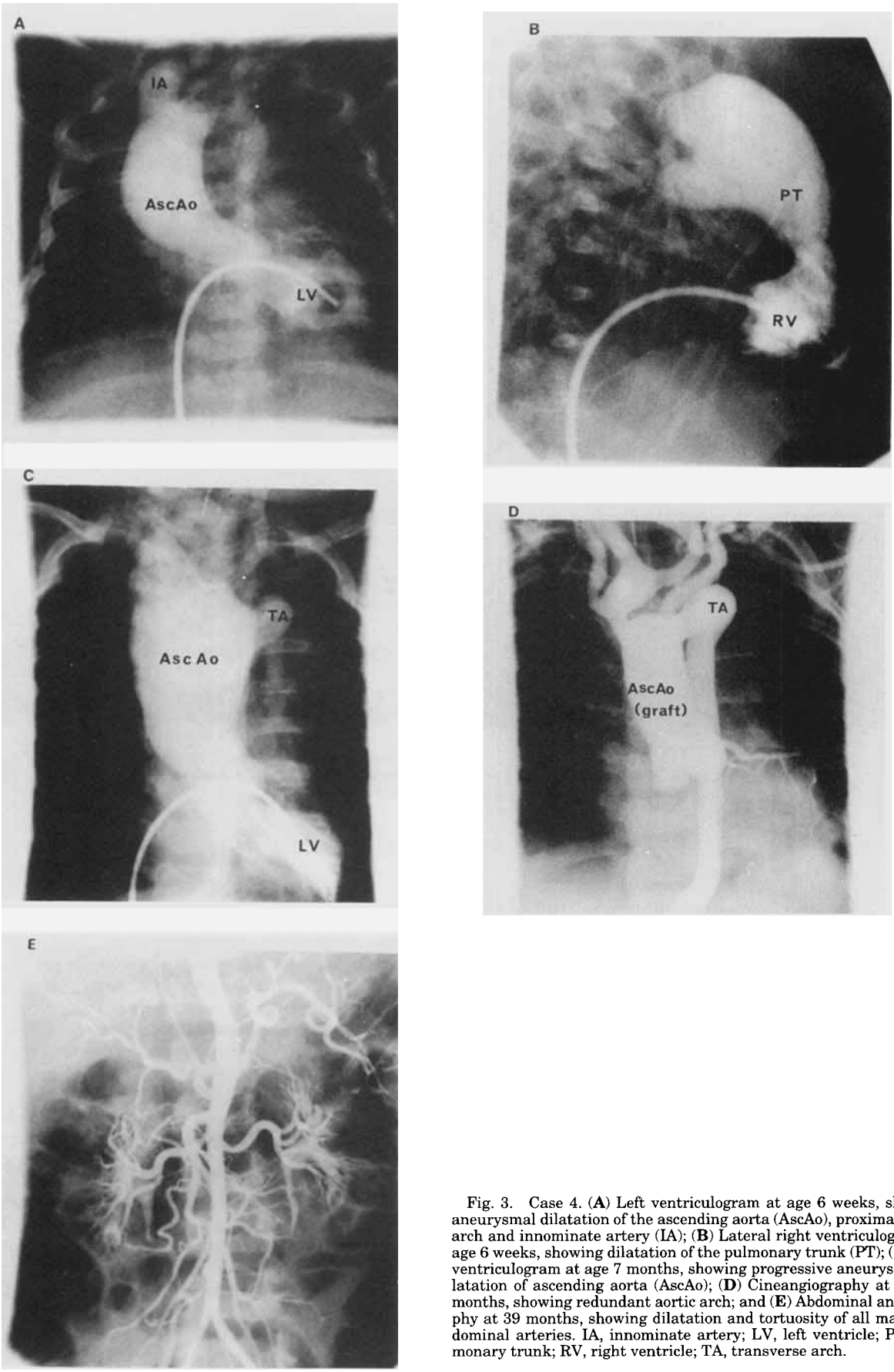

Fig. 3. Case 4. (**A**) Left ventriculogram at age 6 weeks, showing aneurysmal dilatation of the ascending aorta (AscAo), proximal aortic arch and innominate artery (IA); (**B**) Lateral right ventriculogram at age 6 weeks, showing dilatation of the pulmonary trunk (PT); (**C**) Left ventriculogram at age 7 months, showing progressive aneurysmal dilatation of ascending aorta (AscAo); (**D**) Cineangiography at age 39 months, showing redundant aortic arch; and (**E**) Abdominal angiography at 39 months, showing dilatation and tortuosity of all major abdominal arteries. IA, innominate artery; LV, left ventricle; PT, pulmonary trunk; RV, right ventricle; TA, transverse arch.

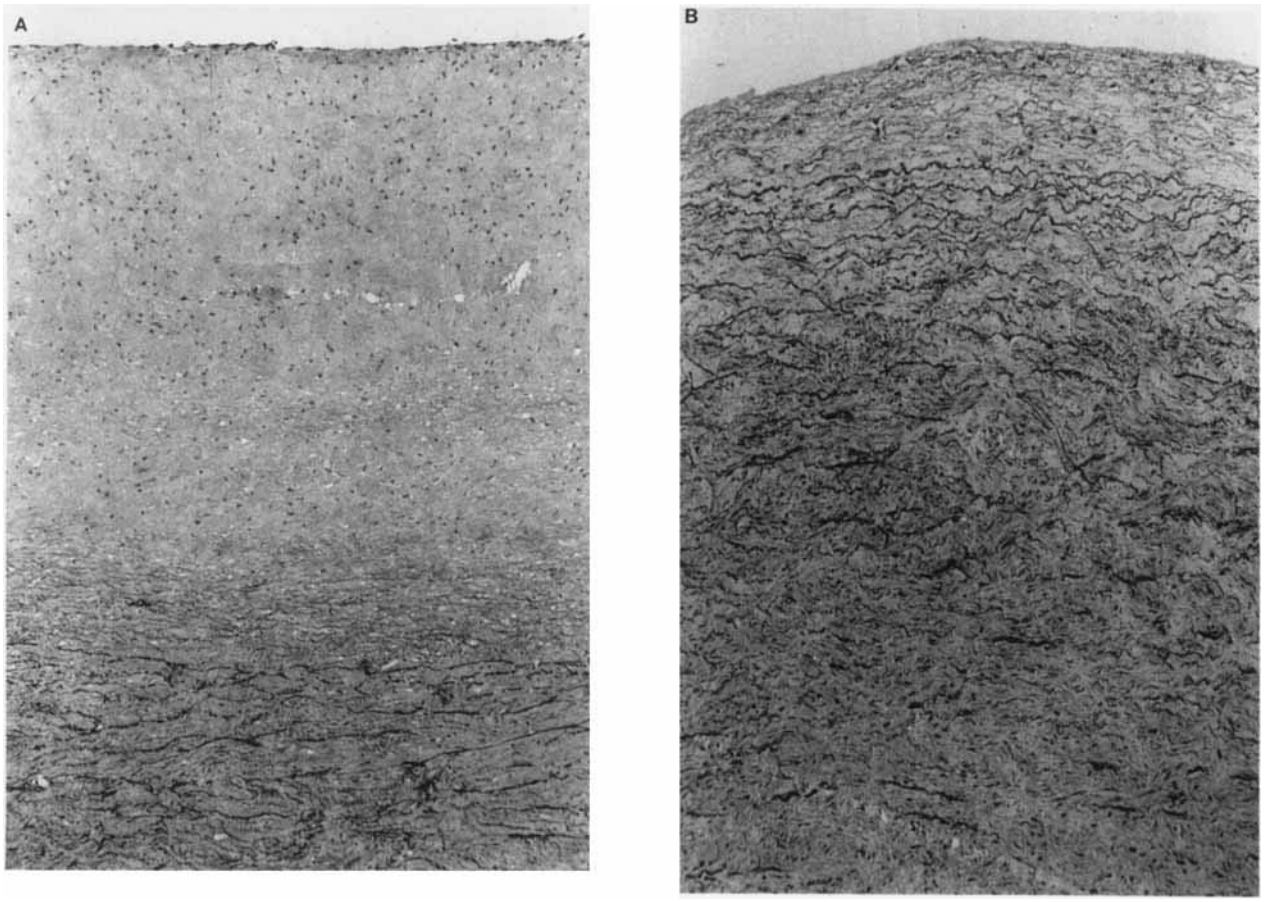

Fig. 4. Case 4. Histological section from the aorta (**A**) and the pulmonary artery (**B**) from initial surgery, showing disruption of elastic fibres, increased deposition of glycosaminoglycans and thickening of the arterial intima. (Movatt pentachrome stain, magnification ×110.)

In Case 4, collagen crosslinking was studied in dermal fibroblasts under conditions that stimulate collagen matrix formation and maturation. While the proportion of the total matrix collagen extracted by pepsin varied in control cells from 32 to 63% of the total collagen, the amount of collagen in Case 4 requiring pepsin extraction fell within this range. Since this collagen fraction requiring pepsin proteolytic extraction represents the insoluble mature crosslinked collagen fraction, these data demonstrate that the proportion of collagen forming mature crosslinks in the patient fell within the normal range in this in vitro system. The proportion of collagen β-components (crosslinked α-chain dimers) was also the same in fibroblasts from controls and Case 4. To determine if there was a difference in the kinetics of crosslink formation, a pulse chase experiment was performed. Again, there were no detectable differences between controls and Case 4, with 79% of the pulse labelled collagen forming an insoluble crosslinked matrix requiring pepsin extraction within 24 hours (Table III).

In addition, fluorescent in situ hybridisation in Case 4 did not demonstrate an elastin gene deletion.

DISCUSSION

Congenital aortic aneurysms are rare, manifesting as single or multiple aneurysms of the thoracic or abdominal aorta. Least common are congenital abdominal aortic aneurysms unassociated with systemic connective tissue diseases or factors specifically implicated in aneurysm development [Darden et al., 1984]. The aneurysms may occur in association with congenital heart disease, multiple peripheral and visceral arterial aneurysms [Burnett et al., 1973; Williams, 1975; Imahori et al., 1969; Short, 1978], tuberous sclerosis (Darden et al., 1984; Hagood et al., 1976; Dutton et al., 1975], neonatal Marfan syndrome (Morse et al., 1990], or cystinosis [Straver, 1979]. Our cases show a unique combination of congenital aneurysms of both the great vessels, with associated arterial abnormalities. These are compared and contrasted with similar reports in the literature in Table IV.

There are three reports in the literature of congenital abdominal aortic aneurysms [Howorth, 1967; Saad and May, 1991; Latter et al., 1989] and an additional two cases of idiopathic abdominal aortic aneurysms in young children [Gibson, 1946; Takayanagi, 1983].

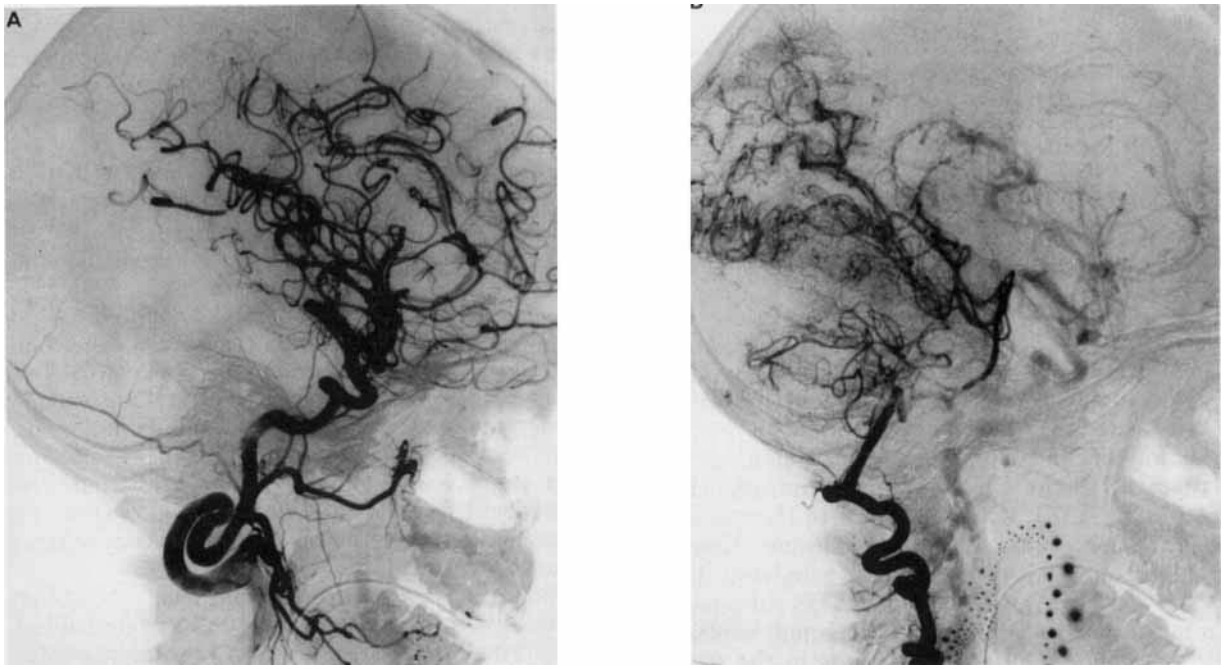

Fig. 5. Case 4. Cerebral angiogram at age 5.5 years. (**A**) Subtraction lateral projection: left carotid angiogram showing diffuse redundancy and tortuosity of the internal carotid, anterior, and middle cerebral arteries; (**B**) Subtraction lateral projection: right vertebral artery angiogram showing marked vessel tortuosity.

There are several reports of individuals with varying combinations of congenital aortic aneurysms, multiple congenital peripheral arterial aneurysms, and arterial tortuosity, in the absence of a recognised connective tissue disorder [Williams, 1975; Haynes et al., 1982; Mirza et al., 1979; Schiller et al., 1983; Lepow et al., 1958]. Aneurysm formation of the radial, brachial, popliteal, posterior tibial, hypogastric, iliac, splenic, hepatic, renal, and phrenic arteries has been reported to coexist with aneurysm of the aorta. Symmetrical involvement of the peripheral arteries is commonly noted with multiple congenital aneurysms. Previous authors [Haynes et al., 1982] have suggested that multiple congenital arterial aneurysms, as seen in Cases 1, 3, and 4, should be considered a distinct clinical entity. While it has been suspected that such cases may have in com-

TABLE I. Clinical and Cardiological Findings in Cases 1–4*

	Case 1	Case 2	Case 3	Case 4
Congenital aortic and main pulmonary artery aneurysm	+	+	+	+
Dilatation of other arteries	+ (PDA, LSA)	+ (RBA, LVA, CA, RPA, LPA)	+ (RPA, LPA)	+ (IA, IMA, ICA, ECA)
Tortuosity of aorta	+	−	+	+
Tortuosity of other arteries	−	+	−	+
Other cardiac defect	+ (ASD)	− (ASD)	+	−
Craniofacial dysmorphism	+	+	−	−
Other non-cardiovascular abnormalities	+	+	−	−

* +, present; −, absent; ASD, atrial septal defect; CA, coronary arteries; ECA, extracranial arteries; IA, innominate artery; IMA, internal mammary artery; ICA, intracranial arteries; LPA, left pulmonary artery; LSA, left subclavian artery; LVA, left vertebral artery; PDA, patent ductus arteriosus; RBA, right brachiocephalic artery; RPA, right pulmonary artery.

TABLE II. Arterial Histologic Findings in Cases 2–4

Case	Arterial histology
2	Non-occlusive fibrointimal hyperplasia; thinning and degeneration of media; decreased fragmented elastic fibres
3	Mild fibrointimal hyperplasia; orderly elastin fibres
4	Fibrointimal hyperplasia; marked disruption and reduction of large elastic fibres; irregular distribution of small elastic fibres

mon a basic biochemical defect in collagen biosynthesis resulting in multiple aneurysm formation, this remains to be substantiated.

Abdominal aortic aneurysms in young children have been reported in the Ehlers-Danlos syndrome (EDS) [Burnett et al., 1973; Mirza et al., 1979; Hunter et al., 1982; McKusick, 1972], Marfan syndrome [Houston, 1978], tuberous sclerosis [Dutton and Singleton, 1975], and cystinosis [Straver, 1979]. Some EDS subtypes are due to mutations in Type I or III collagen, whilst the Marfan syndrome is due to mutations in the fibrillin (FBN1) gene. The autosomal dominant disorder, familial aortic aneurysm, is caused by mutations in the Type III collagen (COL3A1) gene in a proportion of cases. Aneurysmal rupture and death has occurred in a teenager in one such family [Kontusaari et al., 1990]. Aneurysms of the thoracic aorta, and rarely, aortic dissection, have been reported in neonatal Marfan syndrome [Morse et al., 1990]. There has been one recent report of congenital aneurysms of the proximal aorta and pulmonary artery in neonatal Marfan syndrome [Putnam et al., 1996]. Excluding this report, congenital aneurysms of both the aorta and the main pulmonary artery have not been described in any of the aforementioned case reports or in recognised syndromes, and a search of POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations) and LDDB (London Dysmorphology DataBase) did not identify similar cases.

Aneurysm of the ductus arteriosus was an interesting finding in Case 1. Ductal aneurysms previously described [Martin, 1827; Chang et al., 1987] have not been associated with similar congenital abnormalities and pulmonary artery dilatation. However, one female infant with aneurysmal dilatation of the ductus arteriosus and a dilated aortic root, had additional non-cardiovascular abnormalities comprising an inguinal and an umbilical hernia, hyperextensible thin skin, joint hyperextensibility, frontal bossing, apparently low-set ears, hypertelorism, and a highly arched palate [Chang et al., 1987]. Biochemical confirmation was not presented but the authors reported this as a case of EDS. In Case 1 in our series, there were no demonstrable Type III collagen or fibrillin defects.

Case 2 had minor craniofacial anomalies, a retinal hamartoma, a cleft palate, strabismus, abnormal mobility of the large bowel and pectus excavatum in association with aortic root dilatation, pulmonary artery dilatation and arterial tortuosity. Tuberous sclerosis was considered because of the presence of retinal hamartoma. However, the other stigmata of tuberous sclerosis were absent. In addition, pectus deformity is not a manifestation of the condition and arterial abnormalities occur only rarely.

Menkes disease, a disorder of copper metabolism associated with arterial tortuosity, was excluded in Case 3 by normal serum copper, serum caeruloplasmin, and urinary copper excretion results. Homocystinuria was excluded by the absence of urinary homocystine. Histologic changes of the resected aorta were non-specific and unhelpful in terms of establishing a diagnosis.

Case 4 appears unique though there are several reports of cases with similar anomalies (Table IV). Imahori et al. [1967] described what appears to be the first case of EDS, type IV, with arterial tortuosity and multiple aneurysms. Histologic examination showed structural abnormalities in the media of the muscular arteries. Burnett et al. [1973] reported the case of an 8-year-old girl with a saccular aneurysm of the left brachial artery and the right antecubital fossa. She developed two saccular aneurysms of the aorta by age 17 years. Histologic examination of the resected aorta showed defects in the quantity and structural formation of the elastic fibres. The authors reported this as the first recognised case of a major vascular abnormality in the benign form of EDS although there was no biochemical confirmation of the diagnosis. Lees et al. [1969] described a young girl with characteristic clinical and histological findings of EDS, multiple severe peripheral pulmonary artery stenoses, and tortuosity of

TABLE III. Collagen Extraction From Fibroblast In Vitro Matrix*

	(a) Collagen matrix extraction				(b) Pulse-labelled collagen distribution			
	Case 4	C1	C2	C3	Case 4	C1	C2	C3
% collagen in acetic acid extract	57	63	37	32	18	29	20	9
% collagen in pepsin extract	43	37	63	68	79	66	64	85
% β-dimers	20	16	15	20	17	23	16	9

* Fibroblasts were grown in the presence of ascorbic acid for 20 days and the in vitro matrix was (a) serially extracted and the proportions in acetic acid extract (newly crosslinked collagen), and pepsin extract (mature crosslinked collagen) was quantified and expressed as a proportion of the total collagen. The proportion of collagen crosslinked in β-dimers was also calculated. (b) After pulse labelling for 24 hrs and a 24 hr chase period the distribution of the newly synthesised labelled collagen in each extracted fraction, and in β-dimers, was quantified. C1, C2, and C3 represent age-matched controls.

TABLE IV. Summary of Reported Cases: Aneurysms of the Great Vessels, Vascular Abnormalities and Cardiac Defects*

Author	Case	Age (years)	Sex	Vessel abnormality: Aneurysm Aorta	Aneurysm MPA	Aneurysm Other	Dilated arteries	Elongated/ tortuous arteries	Congenital heart defect
Williams	1	5	M	+	–	+	–	–	–
Shohet et al.	1	10	M	+	–	–	–	–	–
	2	11	M	+	–	–	–	–	–
Ertugrul	1	10	F	+	–	–	–	+	–
Beuren et al.	1	1.5	M	–	+	+	–	+	MPAS
Sacks et al.	1–12	Not stated	M,F	+	–	+/–	+	+/–	Congenital arterio-venous fistula in 1 case
Imahori et al.	1	42	F	+	–	+	+	+	–
Burnett et al.	1	8	F	+	–	–	–	–	–
Lees et al.	1	1	F	–	–	–	+	+	MPAS
Adès et al.	1	Newborn	M	+	+	+	–	+	PDA, ASD
	2	Newborn	M	+	+	–	+	+	–
	3	Newborn	M	+	+	+	–	–	PDA,ASD
	4	Newborn	F	+	+	+	+	+	–

* MPA, main pulmonary artery; MPAS, multiple peripheral pulmonary artery stenoses; PDA, patent ductus arteriosus; ASD, atrial septal defect.

the aorta and coronary arteries. Histologic examination of the pulmonary artery showed an increase in elastic fibres in the media, with similar changes noted in the skin biopsy.

Williams [1975] reported a case of multiple aneurysms in childhood, without any reference to EDS. This boy had a large abdominal aortic aneurysm and multiple aneurysms involving the radial, left brachial, right renal, left intrarenal, and common iliac arteries. Histologic examination of the left renal artery showed a normal internal elastic lamina with an abnormal media. The outer third of the media was replaced by collagen and there was an increase in mucopolysaccharide. Appearances were of the "subadventitial fibrosis" type of fibromuscular dysplasia although the patient may have had a mild form of EDS. Shohet et al. [1987] reported a child with hyperextensible skin, moderate joint hypermobility, a large thoracic aortic aneurysm and severe aortic valve insufficiency. Biochemical studies did not show a type III collagen synthesis defect.

Ertugrul [1967] reported the case of a girl with tortuosity and elongation of the aorta, carotid, iliac, femoral, splenic, hepatic, renal and intercostal arteries, a fusiform aneurysm of the descending aorta, and aortic valvular insufficiency. She had telangiectasia of the cheeks and a highly arched palate, but no other findings to suggest a connective tissue disorder. Arterial biopsy showed fragmentation of the internal elastic lamina. Investigations excluded a diagnosis of syphilis, arteriosclerosis, hypertension, mucopolysaccharidosis, and defects of amino acid metabolism. The authors concluded that the diffuse arterial tortuosity and lengthening was likely to be caused by a congenital defect of the elastic tissues of the arterial system. Beuren et al. [1969] reported the case of a young boy with generalised tortuosity and lengthening of all major arteries, including the main pulmonary and coronary arteries. Pathologic changes were confined to the elastic and proximal muscular arteries. The wall of the aorta was thickened, with an increase in the elastic fibres. Similar changes were present in the main pulmonary artery. In the large muscular arteries, there was thickening of the intima with hyperplasia of the elastic fibres and degenerative fragmentation of the internal elastic lamina. The walls of the coronary arteries were thickened and their lumina were narrowed. The authors presumed that their patient had the same disease described by Ertugrul [1967] although there were some differences in the clinical features and in the microscopic findings of the elastic fibres in these two patients. Pseudoxanthoma elasticum was excluded on histological examination of the skin.

The progressive arterial tortuosity and dilatation in Case 4 could be accounted for by homocystinuria, EDS types IV or VI. The former was excluded by the absence of homocystine in the urine. Types I and III collagen were normal, excluding type IV EDS. Collagen crosslinking abnormalities were also excluded. There were none of the clinical features of EDS VI and although lysyl hydroxylase activity was not measured in cultured fibroblasts, this diagnosis seems unlikely. Case 4 showed similarities to the case reported by Ertugrul [1967], although in the latter there was no arterial or main pulmonary artery aneurysm and arterial biopsy showed a decrease of the external elastic membrane and fragmentation of the internal elastic lamina. Aortic histology of Case 4 showed marked thickening of the aortic wall due to a combination of intimal proliferation and deposition of interstitial material between elastic fibres within the media. There was severe disruption and irregularity of the vessel wall elastic lamina. Similar changes were seen in the pulmonary arteries. Case 4 also differed from that described by Beuren et al. [1969] as this child had no dilatation of the main pulmonary artery. He died at 1.5 years from coronary insufficiency and multiple severe peripheral pulmonary stenoses. Arterial histology showed an increase in elastic fibres.

SUMMARY

We describe four unrelated children ranging in age from 2.5 to 7 years, with congenital aneurysms of the great vessels and associated arterial vessel abnormalities. To our knowledge, these clinicopathologic findings have not been reported before. Although one child has died, there were no episodes of arterial dissection or rupture. Contrary to the poor prognosis at birth, these patients seem to survive past the neonatal period. In view of this, conservative management may be the most appropriate course to follow, despite the alarming angiographic appearance of the vessels. Two children (Cases 1 and 2) had some signs of a connective tissue disorder, and arterial elastic fibre abnormalities were present in two children (Cases 2 and 4). The pathogenesis of these aneurysms may be due to an abnormality in the elastic fibre system, but, overall, the histologic findings were heterogeneous and non-diagnostic. Despite intensive investigations, no underlying cause could be identified for the aneurysms that developed in these children.

A clinicopathologic classification of arterial aneurysms in children has been hampered by the rarity of these lesions and failure to identify an underlying aetiology in many cases. The pathophysiological mechanisms and natural history of congenital aortic anomalies, including aneurysms of "idiopathic" origin and multiple congenital arterial aneurysms, are not well understood. When such cases occur, an intensive effort should be made to identify any possible underlying biochemical abnormality as seen in Ehlers-Danlos syndrome, neonatal Marfan syndrome, or Menkes disease. However, the contribution of these disorders to the occurrence of congenital aneurysms of the great vessels and other arterial aneurysms is not known.

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REFERENCES

Bateman JF, Golub S (1994): Deposition and selective degradation of structurally abnormal type I collagen in an in vitro collagen matrix produced by osteogenesis imperfecta fibroblasts. Matrix Biol 14:251–262.

Bateman JF, Harley V, Chan D, Cole WG (1988): Comprehensive analysis of collagen metabolism in vitro using $^{3}H/^{14}C$ proline dual-labelling and polyacrylamide gel electrophoresis. Anal Biochem 168:171–176.

Beuren AJ, Hort W, Kalbfleisch H, Müller H, Stoermer J (1969): Dysplasia of the systemic and pulmonary arterial system with tortuosity and lengthening of the arteries. A new entity, diagnosed during life, and leading to coronary death in early childhood. Circulation 39:109–115.

Burnett HF, Bledsoe JH, Char F, Williams GO (1973): Abdominal aortic aneurysmectomy in a 17-year-old patient with Ehlers-Danlos syndrome: Case report and review of the literature. Surgery 74: 617–620.

Chang JP, Chang CH, Sheih MJ (1987): Aneurysmal dilatation of patent ductus arteriosus in a case of Ehlers–Danlos syndrome. Ann Thorac Surg 44:656–657.

Chen SC, Barner HB, Fagan FL, Kaiser GC, Gerard Mudd JF, Willman VL (1976): Aortic aneurysms in childhood: Report of six instances. J Pediatr 89:231–234.

Darden WA, Fulenwider JT, Smith RB, Whitaker Sewell C (1984): Congenital abdominal aortic aneurysms: Report of a case and review of the literature. Surgery 96:567–573.

Dutton RV, Singleton EB (1975): A case report with aortic aneurysm and unusual rib changes. Pediatr Radiol 3:184–186.

Ertugrul A (1967): Diffuse tortuosity and lengthening of the arteries. Circulation 36:400–407.

Fricker FJ, Park SC, Neches WH, Mathews RA, Lerberg DB (1979): Aneurysm of the aorta in children. Chest 76:305–309.

Gibson TA (1956): Aneurysm of the lower abdominal aorta with rupture in a sixteen month old infant. Am J Dis Child 71:654–658.

Hagood CA, Garvin DD, Lachina FM, Polsky WS, Ball TP, Bobroff LM (1976): Abdominal aortic aneurysm and renal hamartoma in an infant with tuberous sclerosis. Surgery 79:713–715.

Haynes CD, Smith RB, Dempsey RL, Darden WA Jr (1982): Multiple congenital aneurysms associated with spontaneous vascular rupture. Surgery 92:910–912.

Houston HE (1978): Abdominal aortic aneurysm in Marfan's syndrome. J Ky Med Assoc 76:492–493.

Howorth MB (1967): Aneurysm of abdominal aorta in the newborn infant: Report of a case. N Engl J Med 276:1133–1134.

Hunter GC, Malone JM, Moore WS, Misiorowski RL, Chvapil M (1982): Vascular manifestations in patients with Ehlers-Danlos syndrome. Arch Surg 117:495–498.

Imahori S, Bannerman RM, Graf CJ, Brennan JC (1969): Ehlers-Danlos syndrome with multiple arterial lesions. Am J Med 47:967–976.

Kontusaari S, Tromp G, Kuivaniemi H, Ladda RL, Prockop DJ (1990): Inheritance of an RNA splicing mutation ($G^{+1\,IVS20}$) in the type III procollagen gene (COL3A1) in a family having aortic aneurysms and easy bruisability:Phenotypic overlap between familial arterial aneurysms and Ehlers-Danlos syndrome type IV. Am J Hum Genet 47:112–120.

Latter D, Beland MJ, Batten A, Tchervenkov CI, Dobell ARC (1989): Congenital abdominal aortic aneurysm. Canadian J Surg 32: 135–138.

Lees MH, Menashe VD, Sunderland CO, Morgan CL, Dawson PJ (1969): Ehlers-Danlos syndrome associated with multiple pulmonary artery stenoses and tortuous systemic arteries. J Pediatr 75:1031–1036.

Lepow H, Chu F, Muren O (1958): Multiple aneurysm formation. Am J Med 24:631–637.

Martin M (1827): Une dilatation anévrysmale du canal arteriél d'un enfant. Bull Soc Anat Paris (abstr) 2:2.

McKusick VA (1972): The Ehlers-Danlos syndrome. In "Heritable Disorders of Connective Tissue," 4th ED, St Louis: C.V. Mosby, Inc., pp 292–371.

Milewicz DM, Pyeritz RE, Crawford ES, Byers PH (1992): Marfan syndrome: Defective synthesis, secretion, and extracellular formation of fibrillin by cultured dermal fibroblasts. J Clin Invest 89:79–86.

Mirza FH, Smith PL, Lina WN (1979): Multiple aneurysms in a patient with Ehlers-Danlos syndrome: Angiography without sequelae. Am J Radiol 132:993–995.

Morse RP, Rockenmacher S, Pyeritz RE, Sanders SP, Bieber FR, Lin A, MacLeod P, Hall B, Graham Jr JM (1990): Diagnosis and management of infantile Marfan syndrome. Pediatrics 86:888–895.

Procopis P, Camakaris J, Danks DM (1981): A mild form of Menkes steely hair syndrome. J Paediatr 98:97–99.

Putnam EA, Cho M, Zinn AB, Towbin JA, Byers PH, Milewicz DM (1996): Delineation of the Marfan phenotype associated with mutations in exons 23 through 32 of the FBN1 gene. Am J Med Genet 62:233–242.

Saad SA, May A (1991): Abdominal aortic aneurysm in a neonate. J Pediatr Surg 26:1423–1424.

Sacks JG, Lindenburg R (1969): Dolicho-ectatic intracranial arteries: Symptomatology and pathogenesis of arterial elongation and distention. John Hopkins Med J 125:95–106.

Schiller M, Gordon R, Shifrin E, Abu-Dalu K (1983): Multiple arterial aneurysms. J Pediatr Surg 18:27–29.

Shohet I, Rosenbaum I, Frand M, Duksin D, Engelberg S, Goodman RM (1987):Cardiovascular complications in the Ehlers-Danlos syndrome with minimal external findings. Clin Genet 31:148–152.

Short DW (1978): Multiple congenital aneurysms in childhood: Report of a case. Br J Surg 65:509–512.

Skandalakis JE, Edwards BF, Gray SW, Davis BM, Hopkins WA (1960): Coarctation of the aorta with aneurysm. Surg Gynecol Obstet 111:307–326.

Straver DS (1979): Cystinosis and a dissecting aortic aneurysm in a 7-year-old boy. Am J Dis Child 133:436–437.

Takayanagi K, Al-Bader M, Kuwait S (1983): Ruptured abdominal aortic aneurysm in a 7-year-old girl. J Pediatr Surg 18:193–195.

Williams JL (1975): Multiple aneurysms in a child. Proc R Soc Med 68: 523–525.